Proposed Decision Memo for Home Use of Oxygen to Treat Cluster Headache (CAG-00296R)

Decision Summary

CMS proposes that the evidence does not demonstrate that the home use of oxygen to treat cluster headache improves health outcomes in Medicare beneficiaries with cluster headache (CH). Therefore, we propose that home use of oxygen to treat CH is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act). However, we believe the available evidence suggests that the home use of oxygen to treat CH is promising and supports further research under §1862(a)(1)(E) of the Act through the Coverage with Study Participation (CSP) form of Coverage with Evidence Development (CED). Therefore, we are proposing the following decision:

Home use of oxygen to treat CH is covered by Medicare only when furnished to Medicare beneficiaries who have had at least five severe[1] to very severe unilateral headache attacks lasting 15-180 minutes when untreated. The headaches must be accompanied by at least one of the following findings:

1. ipsilateral conjunctival injection and/or lacrimation; or
2. ipsilateral nasal congestion and/or rhinorrhea; or
3. ipsilateral eyelid edema; or
4. ipsilateral forehead and facial sweating; or
5. ipsilateral miosis and/or ptosis; or
6. a sense of restlessness or agitation.

The home use of oxygen to treat CH is covered by Medicare only for beneficiaries with CH participating in an approved prospective clinical study comparing normobaric 100% oxygen (NBOT) with at least one clinically appropriate comparator for the treatment of CH. The clinical study must address one or more aspects of the following questions:

1. Prospectively, compared to individuals with cluster headache who do not receive NBOT, do Medicare beneficiaries with CH who receive NBOT have improved outcomes as indicated by:

a. Pain relief
b. Time to pain relief
c. Durability of pain relief

2. Prospectively, among Medicare beneficiaries with cluster headache, which method of oxygen delivery provides the most benefit as indicated by:
   a. Pain relief
   b. Time to pain relief
   c. Durability of pain relief
3. Prospectively, among Medicare beneficiaries with cluster headache, what other factors, if any, predict the patient's response to 100% oxygen therapy as indicated by:
   a. Pain relief
   b. Time to pain relief
   c. Durability of pain relief

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

(http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

This decision does not, aside from the use of home oxygen to treat cluster headache, modify the existing requirements for coverage of oxygen currently identified in Section 240.2 and Section 240.2.1. The scope of this proposed decision does not include any consideration of hyperbaric oxygen (HBO) for any indication.

We are requesting public comments on this proposed determination pursuant to section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

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TO: Administrative File: (CAG #00296R)
Home Use of Oxygen to Treat Cluster Headaches

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SUBJECT: Proposed Decision Memorandum for Home Use of Oxygen to Treat Cluster Headache (CAG-00296R)
DATE: October 8, 2010

I. Proposed Decision

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We are requesting public comments on this proposed determination pursuant to section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

II. Background

Terminology

For clarity, we note the meanings of the following terms used in this background section. Lacrimation refers to tearing up (crying) of the eyes; rhinorrhea is a runny nose; ptosis refers to eyelid droopiness; miosis is constriction (closing down) of the pupil in the eye. Ipsilateral means same sided, in contrast to contralateral which refers to opposite sided. Edema refers to fluid accumulation or swelling. Normobaric oxygen treatment means treatment at one atmosphere pressure (NBOT). Hyperbaric means treatment at more than one atmosphere pressure (HBOT).

Introduction

Cluster headache (CH), as described in Harrison's Principles of Internal Medicine 16th edition, is an episodic (most common), or chronic unilateral headache syndrome that begins with one to three short-lived headaches per day over many weeks followed by a period of remission. There may be a regular recurrence in the vast majority of attacks. When it becomes chronic, it is characterized by the absence of sustained periods of remission. Generally the cause is unknown but associations can occur with alcohol use which is the only known dietary trigger of CH. There are other triggers such as strong odors (mainly solvents and cigarette smoke) and napping. CH is also characterized by unilateral, excruciating pain principally in ocular, frontal and temporal areas, as well as ipsilateral lacrimation, conjunctival injection, photophobia and nasal stuffiness. Attacks may happen at precise hours, especially at night. During the attacks, patients tend to be restless.

CH is associated with trigeminovascular activation[2] and neuroendocrine[3] and vegetative disturbances[4], however, the precise causative mechanisms remain unknown. The hypothalamus is thought to be the site of activation for the disorder. Diagnosis is based on clinical findings and differential diagnosis includes other primary headache diseases such as migraine, paroxysmal hemicranias and SUNCT (short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) syndrome. The disease course is unpredictable over a patient's lifetime. Some patients have only one period of attacks, while in others the disease evolves from episodic to chronic form. Though there is no known cure for the syndrome, many patients experience spontaneous discontinuation of the headaches.

Epidemiology

CH affects young adults, predominantly males, with a seven to one male to female ratio. Prevalence is estimated at 0.05-0.4 percent in the general population of the U.S. The disease is familial in about ten percent of cases. Genetic factors may play a role in CH susceptibility, and a causative role has been suggested for the hypocretin receptor gene. The table in Appendix A adapted from LeRoux et al. (2008), a review of CH prevalence studies from a number of specified countries, indicates a prevalence range from about 0.05 percent to 0.4 percent.

Diagnostic criteria

The following are the criteria used by the International Headache Society to make a definitive diagnosis:

A. At least 5 attacks fulfilling criteria B-D

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated

C. Headache is accompanied by at least one of the following:
   1. ipsilateral conjunctival injection and/or lacrimation
   2. ipsilateral nasal congestion and/or rhinorrhea
   3. ipsilateral eyelid edema
   4. ipsilateral forehead and facial sweating
   5. ipsilateral miosis and/or ptosis
   6. a sense of restlessness or agitation

D. Attacks have a frequency from one every other day to 8 per day
E. Not attributed to another disorder

Treatment

The medical literature includes anecdotal reports of the use of 100% normobaric and hyperbaric oxygen for the treatment of CH. Oxygen is an odorless, colorless gas at room temperature. It can be delivered in a chamber, by compressed air, via oxygen concentrator, or other method. Though often thought of as harmless, oxygen use has been noted to have adverse effects including blindness, pulmonary fibrosis, and suppression of the drive to breathe in patients who have advanced chronic obstructive lung disease (Patel et al. 2003). Oxygen is also known to increase fire risk in certain environments. There are a number of drug treatments for CH, including but not limited to IV and sublingual sumatriptan. Effective prophylactic drugs include prednisone, lithium, Methysergide, ergotamine, sodium valproate, and verapamil. At present, there is no curative treatment.

III. History of Medicare Coverage

Medicare has a National Coverage Determination on the Home Use of Oxygen (NCD 240.2). The NCD states the home use of oxygen is reasonable and necessary for patients with significant hypoxemia, as evidenced by a blood gas study or a measurement of arterial oxygen saturation. In 2006, an internally generated NCD led to coverage with study participation for those beneficiaries who did not qualify for coverage based on the initial criteria for hypoxemia established in the earlier NCD (240.2.1). This expansion in coverage requires that beneficiaries be enrolled subjects in clinical trials sponsored by the National Heart, Lung, and Blood Institute (NHLBI). Current national policy states that the Home Use of Oxygen is reasonable and necessary for only those patients diagnosed with significant hypoxemia in conjunction with certain health conditions.

<u>Current Request</u>

CMS has received complete requests from Fred Sheftell, MD, President, American Headache Society; Robert C. Griggs, MD, FAAN, President, American Academy of Neurology.

The scope of this review does not include any consideration of hyperbaric oxygen therapy (HBOT) for any indication.

Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage, § 1812 (Scope of Part A); § 1832 (Scope of Part B) § 1861(s) (Definition of Medical and Other Health Services). Provided that all coverage requirements are met, Medicare covers home use of oxygen as a supply to durable medical equipment (DME), which is referenced in section 1861(s)(6) of the Social Security Act. Thus, the home use of oxygen falls within the DME benefit category.

IV. Timeline of Recent Activities

April 9, 2010	CMS posts a tracking sheet and opens a National Coverage Determination (NCD) reconsideration to determine if there is sufficient evidence to change the policy. Currently, CMS has a non-coverage policy for the Home Use of Oxygen when used to treat CH. The initial 30-day public comment period begins.
May 9, 2010	Initial public comment period ended. CMS received a total of 65 comments.

V. FDA Status

Oxygen itself is a naturally occurring element, readily available commercially from a variety of industrial and other sources. While the FDA regulates the equipment and delivery systems required for providing oxygen therapy, it does not regulate the use of oxygen.

VI. General Methodological Principles

In general, when making NCDs under §1862(a)(1)(A), CMS evaluates relevant clinical evidence to determine whether or not the evidence supports a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or improves the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for Medicare beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary under § 1862(a)(1)(A) of the Act.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence we considered during our review. The evidence reviewed to date in this NCD includes the published medical literature on pertinent clinical trials of home oxygen for treatment of CH.

B. Discussion of Evidence Reviewed

1. Questions

a. Is the evidence adequate to conclude that the home use of oxygen improves health outcomes in Medicare beneficiaries with cluster headache?

b. If the answer to question a. is yes, what factors predict a favorable or unfavorable response to treatment?

2. External Technology Assessment:

An external technology assessment was not commissioned for this review.

3. Internal Technology Assessment

Systematic reviews are based on a comprehensive search of published studies to answer a clearly defined and specific set of clinical questions. A well-defined strategy or protocol (established before the results of the individual studies are known) guides this literature search. Thus, the process of identifying studies for potential inclusion and sources for finding such articles is explicitly documented at the start of the review. Finally, systematic reviews provide a detailed assessment of the studies included.

Literature search methods

We searched the MEDLINE database, the Cochrane Library, the National Guidelines Clearinghouse, and the International Network of Agencies for Health Technologies Assessment (INAHTA) database and performed a hand search of bibliographies included in the articles. Search criteria used the terms oxygen or O_2, cluster headache, and identified those with and without RCT design. Of the 138 references found there were four articles that met methodologic criteria for further review. All four were systematic reviews or reports of randomized controlled trials (RCTs). The remaining papers often referred anecdotally to home oxygen use for CH, referred to one of the above four papers, or involved the use of specific medications for the treatment of CH.

Systematic Review

Bennett et al. Cochrane (2009): Normobaric and hyperbaric oxygen therapy for migraine and Cluster Headaches (Systematic review of RCTs).

Country: Australia, Germany
Disease studied: CH
Study type: Systematic review of RCTs for treatment of CH
N= 2 RCTs for NBOT
Study focus: Oxygen treatment for migraine and CH
Modalities compared: NBOT vs. sham, and NBOT vs. ergotamine
Primary outcome measure(s): Termination of CH
Age ≥ 65: Yes
M:F: NA
Race/Ethnicity reported/analyzed: No

The purpose of this review was to assess the evidence of HBOT and NBOT for treating and preventing migraine and CHs. They included randomized trials comparing HBOT or NBOT with one another, other active therapies, placebo (sham) interventions or no treatment in patients with migraine or CH. Three reviewers independently evaluated study quality and extracted data. Only two small trials were found that evaluated NBOT for CH (Kudrow, Fogan, see below). NBOT was effective in terminating CH compared to sham (air) in a single small (N = 19) study, Fogan, (RR 7.88, 95% CI 1.13 to 54.66, P = 0.04) in which the systematic review reported that each participant had *at least* six headache episodes for both the oxygen and air treatments at 6L/mi (according to the table published with the review), but not superior to ergotamine administration in another small trial (RR 1.17, 95% CI 0.94 to 1.46, P = 0.16). Seventy-six per cent of patients responded to NBOT in these two trials, according to the review. No serious adverse effects of NBOT were reported. We note that in the original report of the Fogan study each participant actually had *at most* six headache episodes, not *at least*. Based on the authors' findings they concluded that there was some evidence that oxygen was effective in the treatment of CH.

Randomized Controlled Trials (RCTs)

Cohen et al. (2009): High-Flow Oxygen for Treatment of Cluster Headaches: A Randomized Trial.

Country: UK
Disease studied: CH
Study type: RCT - crossover
N = 76
Study focus: Oxygen for CH
Modalities compared: High flow oxygen (12L/min) vs. placebo (high flow air 12/L)
Primary outcome measure(s): To render the patient pain free from CH at 15 minutes
Age ≥ 65:Yes mean age = 39 (range 18-70 years).
M:F: % Not given
Race/Ethnicity reported/analyzed: No

The purpose of this study was to ascertain whether high-flow inhaled oxygen was superior to high flow air (placebo) in the acute treatment of CH. They conducted a double-blind, randomized, placebo-controlled crossover trial of 109 adults (aged 18-70 years) with CH as defined by the International Headache Society. Patients were included in the study if they had episodic or chronic CH and experienced between one attack every other day to five a day and the duration of the attacks was between 45 minutes and three hours. Patients were treated for headache episodes with high flow inhaled oxygen or placebo. Then, during the crossover, they were treated with the alternative.

Patients were selected from support groups across England. They were recruited and followed up between 2002 and 2007 at the National Hospital for Neurology and Neurosurgery, London, England. Randomization pertained to the order in which they received the active treatment or placebo and was described. The interventions were either 100% inhaled oxygen or high-flow air placebo at 12 L/min, delivered by face mask, for 15 minutes at the start of an attack of CH delivered alternately (first one unmarked tank as directed, then the other) for four attacks each intervention. The method of oxygen delivery was described including type and capacity of cylinder, compression of contents, regulator use for standardization, and face mask.

In planning the study, and based on outcomes treatment by intranasal and subcutaneous sumatriptan in CH, the authors determined a 25% difference between placebo and active treatment would be clinically significant. They estimated that 55 patients were needed for a power of 80% with a type 1 error of 5%. A drop-out rate of 15% was allowed for, and therefore 70 patients were to be recruited. Outcome data were treated as binary, that is, success or failure in treating the CH.

A total of 334 patients were assessed for eligibility (225 were excluded: 73 for previous oxygen treatment or chronic migraine; 58 stopped having CH; 37 declined participation; 31 diagnosis unclear; 22 receiving prevention; 4 for other reasons) and 109 were randomized between March 2003 and April 2007. Of these 109, 33 did not receive treatment for the following reasons: 17 stopped having CH; nine lost to follow-up; six withdrew from study; one died before receiving treatment. That left 76 subjects, 57 with episodic and 19 with chronic CH, all of whom were included in the analysis.

Total time of the study was to be five years. The study was performed in the patient's home with two gas containers labeled "treatment 1" and "treatment 2." Randomization of study-eligible patients was performed using opaque sealed envelopes, inside of which was a card labeled "A" or "B," which determined the order the patient received active treatment or placebo. Once the patients had treated four attacks each, they returned the diaries to the investigators and called the gas supplier to collect the cylinders from their homes.

The primary end point was to "render the patient pain free", or in the absence of a diary to have adequate relief, at 15 minutes. For the primary end point the difference in outcome between oxygen, 78% (95% confidence interval, 71%-85% for 150 attacks) and air, 20% (95% confidence interval, 14%-26%; for 148 attacks) was statistically significant (Wald test, Chi sq 5 df =66.7, *P*<.001). There were no reported important adverse events. The authors concluded that treatment of patients with CH at symptom onset using inhaled high-flow 100% oxygen compared with 100% air (placebo) was more likely to result in being pain-free at 15 minutes.

Fogan (1985): Treatment of Cluster Headaches A double-blind comparison of oxygen vs. air inhalation.

Country: USA
Disease studied: CH
Study type: RCT crossover
N= 19
Study focus: Oxygen for CH
Modalities compared: 100% oxygen vs. air at 6L/min
Primary outcome measure(s): The patients' subjective evaluation of CH pain relief
Age ≥ 65: No - mean- age not given (range 20-50 years)
M:F: 100:0%
Race/Ethnicity reported/analyzed: No

The author conducted an acute CH therapy cross-over RCT with allocation concealment and blinding of both patients and investigator. The cross-over was made after up to six episodes of CH were treated with the first assigned gas. Nineteen patients (20 to 50 years, all male) with a diagnosis of CH, according to the Ad Hoc Committee on Classification of Headache 1962, were selected. The stated intention was to do a double-blind crossover study comparing 100% oxygen and air inhalation at 6 L/min via nonrebreathing face masks for 15 minutes or less, for up to six headaches for each treatment.

Eleven of the 19 were successfully crossed to receive both gases, but the remaining eight received only one of the gases (three air, five oxygen). Two were accidentally given the same gas both times, one oxygen and the other air. Patients scored their own degree of relief for each treatment as none, slight, substantial, or complete relief. The author aggregated all the data for each treatment into one group, despite the fact that 8 of 19 patients did not complete the study.

Nine out of 16 patients (56%) who used oxygen reported a complete or substantial relief in 80% or more of their cluster attacks compared with only one of 14 patients (7%) who used air. Six of the patients' CH syndrome disappeared before the end of the trial. The average (± SE) relief score for all oxygen-treated patients was 1.93 ± 0.22 out of a possible total score of 3.0, and for air the treatment relief score was 0.77 ± 0.23. This difference was reported to be highly statistically significant using an analysis-of-variance F test. The author concluded that his results document that patients with CH can benefit from oxygen inhalation during acute attacks.

Kudrow (1981): Response of Cluster Headaches attacks to oxygen inhalation.

Country: USA
Disease studied: CH
Study type: RCT
N = 100
Study focus: Oxygen for CH
Modalities compared: Oxygen, ergotamine
Primary outcome measure(s): Complete or almost complete response and time to success
Age ≥ 65: Not given - mean age = 48.5
M:F: 84:16%
Race/Ethnicity Reported/Analyzed: No

The purpose of this study was to compare treatment of CH with 100% oxygen to sublingual ergotamine tablet by performing a randomized control trial. Fifty persons were randomly selected for a cross-over trial where 25 (Group1) received oxygen at 7L/minute for 10 consecutive CHs and 25 (Group2) received sublingual ergotamine (up to three tablets 15 minutes apart) for 10 consecutive CHs. Then the groups crossed over and reversed treatment for another 10 consecutive CHs (Group2 received oxygen on crossover and Group1 received ergotamine).

Successful response for either oxygen or ergotamine was defined as almost complete, or complete cessation of head pain within 15 minutes, for at least seven of 10 attacks. Regardless of order of treatment and lack of classification of CH into chronic or episodic, 100% oxygen had an 82% success rate compared to 70% for sublingual ergotamine. The average time to success with NBOT was shorter, about six minutes as compared to 12 for sublingual ergotamine. The findings were not found to be statistically significant. When comparing episodic CH patient treatment with oxygen as compared to sumatriptan, there was no statistically significant success difference (77.7% vs. 71.4%) but there was one comparison in favor of oxygen (86.1% vs. 50%) when comparing treatment of chronic CH.

Rapidity of CH relief was similar for oxygen versus ergotamine given a 15 minute time period, but 46% of oxygen treated patients had relief at six minutes as compared to 40% having relief at 12 minutes for ergotamine. The author concluded that 100% oxygen at 7L/min was effective in treating CH. The author further commented that contraindications and/or side effects to oxygen are rare and concluded that oxygen is an excellent way to treat CH.

4. MEDCAC

A Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting was not convened on this issue.

5. Evidence Based Guidelines

We searched for evidence based guidelines that discussed oxygen to abort or prevent CH. Relevant parts are included below.

The online National Guideline Clearinghouse database was searched using the term "cluster headache." One guideline was found, developed by the European Federation of Neurological Societies (EFNS). The guideline was published in the European Journal of Neurology in 2006. The International Headache Society has since adopted the EFNS guideline.

The website for the National Headache Foundation, the American Academy of Neurology, and the Institute for Clinical Systems Improvement (ICSI) were searched using the terms "cluster headache" and "cluster headache guidelines." Guidelines were found on and taken from each organization's website.

The website for the American Neurological Association, American Headache Society, National Institute of Neurological Disorders and Stroke, the American Medical Association, the American Academy of Family Physicians, and the American Society of Internal Medicine were searched using the terms "cluster headache" and "cluster headache guidelines." No guidelines were found.

<u>The European Federation of Neurological Societies (EFNS) Guideline</u>

The guideline prepared by the European Federation of Neurological Societies (EFNS) considers treatment and prevention efforts for cluster headaches. The EFNS taskforce based their guideline on hand searches of published literature and searches of electronic databases. The evidence was graded on a rating scheme where classes range between I and IV, with Class I indicating the strongest evidence and Class IV the weakest. Class I includes a sufficiently powered prospective, randomized, controlled clinical trial with blinded outcome assessment in a representative population, or, a sufficiently powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. Class II represents a prospective matched-group cohort study in a representative population with masked outcome assessment that meets the criteria in Class I, or a controlled trial in a representative population that lacks a criterion stated in Class I. Class III includes all other controlled trials in a representative population, where outcome assessment is independent of patient treatment. Class IV is evidence from uncontrolled studies, case series, case reports, or expert opinion.

The evidence from the studies was evaluated in accordance with recommendations of the EFNS. Findings were given a level A, B, or C recommendation. Level A rating means the recommendation is effective, ineffective, or harmful, and is based on at least one influential class I study or at least two consistent class II studies. Level B rating means the recommendation is probably effective, ineffective, or harmful and requires at least one convincing class II study or overwhelming class III evidence. Level C rating means the recommendation is possibly effective, ineffective, or harmful and requires at least two convincing class III studies.

According to the guidelines, the first choice for the treatment (Level A) of an acute attack should be the inhalation of 100% oxygen with at least 7 liters per minute over a 15 minute period or with the subcutaneous injection of six mg sumatriptan. Nasal sumatriptan or oral zolmitriptan are alternatives, however they take longer to become effective.

Prevention of cluster headache should first employ verapamil at a daily dose of at least 240 mg. Steroid use of at least 100 mg methylprednisone given orally or up to 500 mg intravenously per day over five days is recommended and is effective, although no class I or class II trials are available.

Level B recommendations include intranasal lidocaine and subcutaneous octreotide when level A medication is ineffective or contraindicated. Methysergide and lithium are next in line if lidocaine and subcutaneous octreotide are ineffective or contraindicated. Corticosteroids, topiramate, melatonin and ergotamine tartrate are recommended in certain doses and based on tolerance and individual cases. Pizotifen and intranasal capsaicin have side effects and therefore should rarely be used.

National Headache Foundation

The guideline prepared by the National Headache Foundation considers treatment, prevention, and maintenance efforts for cluster headaches. The guideline is based on searches of electronic databases and the consensus of an advisory panel of practitioners chosen for their expertise. Guidelines are also based on experience in clinical settings.

Oxygen inhalation is the customary treatment for cluster headaches. Inhalation of 100% oxygen at a flow rate of 7-10 liters per minute for 15 minutes is the standard. In most patients, oxygen use is effective, however, in some patients, pain returns and is not completely eliminated. Subcutaneously administered sumatriptan at six mg is most effective for patients who experience one or two cluster attacks per day. Zolmitriptan, dihydroergotamine, nasal lidocaine, and capsaicin are all used for relief, and some are more effective for different patients.

Preventive treatment, meant to repress attacks and to maintain relief through the cluster period, includes the use of corticosteroids and ergotamine derivatives. Maintenance therapy includes: verapamil, methysergide maleate, lithium carbonate, valproic acid, topiramate, and melatonin.

American Academy of Neurology

The "Headaches: Practical Management" guideline developed by the American Academy of Neurology (AAN) lists treatments and prevention options. For symptomatic treatment of cluster headache, the AAN recommends oxygen inhalation. The patient should receive 100% oxygen at seven or more liters per minute with a facemask. The drug DHE-45 preceded by an antiemetic may also provide relief. Subcutaneous injection of sumatriptan is also effective, but the patient must be monitored for risk factors for coronary artery disease because it is a contraindication to the use of sumatriptan. Transnasal butorphanol is another alternative.

For preventive treatment, the authors suggest prednisone for quick control of the episode, but they caution its use because it causes immediate bone loss. Therefore, Vitamin D should be taken as a supplement. Methysergide, verapamil, valproic acid, and lithium are also useful for prevention, but lithium must be monitored for toxicity. For refractory cases, gabapentin, and topiramate might be useful, and combinations of verapamil and lithium, or verapamil and valproic acid may be effective when individuals drugs are not effective. When all other options are exhausted, surgical treatment might be appropriate. Current practice is percutaneous radiofrequency lesions directed against the trigeminal ganglion.

Institute for Clinical Systems Improvement

The ICSI health care guideline for the diagnosis and treatment of headache was updated in March 2009 and is intended as a guideline to assist clinicians for the diagnosis and treatment of patients. This document also included treatment of CH. The Committee for Evidence-based Practice is composed of a group of 6-12 members including physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, and an ICSI staff facilitator. The group conducts a literature search to identify important clinical trials, meta-analysis, systematic reviews, or regulatory statements, as well as other professional guidelines. Then, a critical review process allows the clinicians to thoroughly review the science and make changes to the guideline or approve what is proposed.

Literature is also graded based on design type and quality of the research report. A grade I conclusion is supported by good evidence and consistency of results from studies of strong design, the results are clinically important and consistent, have no significant threats to internal and external validity, few to no flaws in design, and have adequate statistical power. A Grade II conclusion is supported by fair evidence consisting of studies of strong design but with uncertainty due to inconsistencies among the results from the studies or because of minor threats to internal and external validity, research design flaws, or inadequacy of sample size. Grade III studies consist of strong design for answering the question addressed, but include substantial uncertainty in the results because of serious threats to internal and external validity, research design flaws, or inadequacy of sample size.

The ICSI guideline for the diagnosis and treatment of CH headache states that oxygen inhalation is highly effective at 7-15 liters per minute via a face mask. Drugs to treat the acute attack may be hard to attain in proper quantities. Subcutaneous sumatriptan is the most effective self-administered medication for the relief of pain, but it is not effective when used prophylactically. Dihydroergotamine mesylate (DHE) also provides relief.

For bridging treatment of CH, ICSI recommends corticosteroids, ergotamine, or occipital nerve block. For first line maintenance treatment ICSI recommends verapamil. Other maintenance treatments include avoiding alcohol, verapamil in high doses, corticosteroids, lithium, divalproex sodium, or topiramate.

6. Professional Society Position Statements

During the initial comment period, the American Academy of Neurology (AAN) expressed strong support for the use of oxygen to treat cluster headaches. The AAN, a requester of the national coverage determination, recommended that oxygen therapy to treat cluster headache should be used because it can be administered more than once per day, is very effective in eliminating pain, and has minimal to no adverse side effects for the majority of those who are affected. Oxygen is also convenient for the patient because it is easily transported. The AAN recommends oxygen use to abort or reverse an individual attack of cluster headache, especially under the following circumstances: when preventive or abortive therapies are less than entirely effective and breakthrough headaches occur, when preventive or abortive medications are contraindicated or produce adverse effects, when multiple attacks occur during a 24-hour period, making other abortive treatments unacceptable, and in the elderly population where breakthrough attacks must be treated quickly and other potential therapies or medications are unsafe or inappropriate.

7. Expert Opinion

Apart from the public comment process, we have not received any expert opinions on the treatment of CH via home use of oxygen for beneficiaries.

8. Public Comments

As noted above, CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. CMS responses to initial comments are, as customary, incorporated into our analysis.

Initial Comment Period 4/9/2010 – 5/9/10

CMS received a total of 65 comments during the initial 30 day public comment period. Commenters self-identified as organizations, suppliers, physicians, other clinicians and patients. Many comments, 31 in all, were submitted by patients with CH or their advocates. Four comments were submitted by industry, one by a physician professional organization, one by a physician, one by a nurse, and 27 others who did not identify an affiliation.

The American Academy of Neurology (AAN) was the only Physician Professional Organization to submit a formal comment. The AAN urged CMS to allow for the home use of oxygen to treat CH especially for those patients who are treatment resistant, have contraindications to existing therapies, or suffer with breakthrough attacks.

Some stakeholders came in for face-to-face meetings with CMS staff members to express their support for the home use of oxygen to treat CHs. CMS met with representatives from the American Headache Society on July 27, 2010. Two practicing neurologists and their representatives provided us with information on the diagnosis and treatment of cluster headache. These materials included three pages from a textbook entitled, "Wolff's Headache and Other Head Pain" that describes the use of normobaric oxygen to treat cluster headache.

All comments submitted were in favor of Medicare coverage - no one who wrote to CMS opposed coverage. Many comments stated that oxygen has no known adverse events associated with its use in treatment of CH. Others state that treatment with oxygen is especially useful for patients with contraindication to prescription medications. One physician and one nurse wrote in support of coverage based on their experience in administering oxygen for CH in a clinical setting. Industry comments favored the use of hyperbaric oxygen to treat CH, even though the use of hyperbaric oxygen is not considered in this NCD.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury of to improve the functioning of a malformed body member." See § 1862(a) (1) (A) of the Act.

In addition to section 1862(a) (1) (A), a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a) (1) (E), provides, in pertinent part, that:

(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
. . .
(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]
. . .

Section 1142 describes the authority of the AHRQ.

Under the authority of § 1862(a)(1)(E), Medicare may cover under coverage with evidence development (CED)/coverage with study participation (CSP) certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A), and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. CMS has described CED in greater detail in a guidance document available at http://www.cms.gov/mcd/ncpc_view_document.asp?id=8. CED allows CMS to provide coverage based on a determination that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise.

Under section 1142, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically.

For some items or services, CMS may determine that the evidence is preliminary and not reasonable and necessary for Medicare coverage under section 1862(a)(1)(A), but, if the following criteria are met CED might be appropriate:

- The evidence includes assurance of basic safety;
- The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and
- There are significant barriers to conducting clinical trials.

These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

1862(a)(1)(A) Analysis

Questions:

a. Is the evidence adequate to conclude that the home use of oxygen improves health outcomes in Medicare beneficiaries with cluster headache?

b . If the answer to question a is yes, what factors predict a favorable or unfavorable response to treatment?

We extensively reviewed the literature regarding treatment of CH with normobaric oxygen. In this review we found many anecdotal references to the use of this modality for CH but we found only three RCTs that provided some evidence of its impact on health outcomes, specifically on relief of CH symptoms. Other papers referred to one or more of these trials to support a conclusion that normobaric oxygen was helpful in treating CH.

Two of the RCTs were performed in the 1980s. The first of these, and the only one on record until that time was done by Kudrow (1981). The study contained numerous limitations. The method of patient selection was not stated, prior use of medications for treatment of CH was not described, and the definition of CH for this study was not in agreement with current definitions increasing the chance of misclassification of headache type. Furthermore the comparator was sublingual sumatriptan, not inhaled air, no confidence intervals were provided, nor was statistical methodology described. The mean age is not typical of Medicare beneficiaries so we do not know if any persons over 65 were included in the study, and data were not analyzed by sex, though 84% were male. Other limitations included that the duration of the study was not stated in the paper resulting in another question of study design rigor, the prior use of medications before oxygen treatment was not described, the author reported eight successes or more in table 5 but for the same statistic he reported elsewhere in the paper as 'at least seven.' Finally the description of oxygen delivery was minimal except for the fact that 100% oxygen was delivered by cylinder, leaving unanswered the question of standardization of treatment.

Though the flaws of this RCT limit its evidentiary weight and it did not compare oxygen to air we do take note that the 80% CH treatment success rate for 100% oxygen is similar to the rate found in the Cohen et al. study cited by us elsewhere in this memorandum.

In the Fogan study, 19 patients (20 to 50 years, all male) with a diagnosis of CH participated in a double-blind crossover study comparing 100% oxygen versus air inhalation, at 6 L/min, via nonrebreathing face masks for 15 minutes or less, for up to six headaches for each treatment. This study also contained numerous limitations. First, eight of the 19 did not receive both gases (three air, five oxygen). Even though the authors claimed statistical significance in favor of oxygen, there was a methodologic error in the indiscriminate aggregation of data, use of an inappropriate statistical test, and a significant drop-out rate with data loss in this small trial. The description of method of delivery of oxygen did not mention regulator usage and was not as well described as needed, the randomization method was not stated and no power calculation was recorded. Additionally the study had a small number of participants, there was no indication of any exclusion criteria and patients were reportedly instructed not to take prophylactic or pain relief medication, which could result in inaccurate results. The age range is not typical of Medicare beneficiaries, the mean age was not available, and data were not analyzed by sex, though 84% were male. The manner of selection of these patients is not stated and selection bias is relevant. Finally we note that in looking at each patient individually, there was a markedly unequal number of CH tested among all the patients ranging from zero to six with either oxygen or air. All these limitations lead us to assign less evidentiary weight to this study even though it attempted to address the question of NBOT vs. air treatment.

The third and last RCT we found was Cohen et al., reported in 2009. Of 109 subjects considered eligible and randomized (out of 334), 33 did not receive treatment for one reason or another, leaving 76 participants, who ranged in age from 18-70 years. The mean age was reported as 39 years, significantly younger than the general Medicare beneficiary population. For the primary end point of being pain free or having adequate relief within 15 minutes, the difference between oxygen, 78% (95% confidence interval, 71%-85% for 150 attacks) and air, 20% (95% confidence interval, 14%-26%; for 148 attacks) was highly significant. The study contained a few limitations. The gender was reported in the study but males and females were not analyzed separately, therefore we could not determine the treatment effects between males and females and the 33 who did not receive treatment for one reason or another were not included in an intention-to-treat (ITT) analysis. Finally episodic or chronic CH persons were not analyzed separately though there may be a difference in the responsiveness between these two groups, selection of cases bias exists, as only a minority of the potentially eligible subjects were randomized and ultimately accounted for by the completion of the study. That is, selection bias occurred because patients were taken on a convenience basis from a number of CH focus groups across the country. We believe that these limitations reduce the evidentiary weight of this study.

The Cochrane report of RCTs involving normobaric and hyperbaric oxygen therapy for CH mentioned two of the above three RCTs as it was published before the latest one (Cohen et al. 2009) and reported that there was weak evidence to support 100% oxygen for treatment of this entity. The Cochrane report mentioned that the Fogan study involved at least six CH per participant when actually it was less than or equal to six, and in some cases only one or two. Especially in light of an evidence base that is already limited in the first place, we believe that this error significantly diminishes the evidentiary weight that we can attribute to this report.

A number of guidelines referenced in our Guidelines section support the use of oxygen for cluster headaches. Some guidelines included a rating scheme based on trial design and implementation, as well as methodologic rigor, while other guidelines did not. For those that did supply this information, we note that the guidelines do not take age subgroups into consideration. When assessing the effectiveness of an intervention. In general they assess the trials and make an overall determination which is often generalized to all populations. CMS has a special population primarily aged 65 or older. Most of the studies that the guidelines assessed and based their determinations on, did not include persons age 65 or older. This would make the findings of the guidelines hard to generalize to Medicare beneficiaries.

Another reason why guideline determinations may not be applicable to sub-populations (e.g. patients 65 and older), is the heterogeneity of studies upon which the guideline is based. Some studies might be of one design with one group of inclusion/exclusion criteria, and differing statistical techniques, while another group of studies may have a different design, different inclusion/exclusion criteria, and use a different statistical technique. If guidelines were based on meta-analysis, using studies consisting of homogeneous populations, similar inclusion/exclusion criteria, and the same statistical technique, then results of the findings would be more likely to show the true association between variables being explored. A main limitation of all these guidelines is that they use the limited medical literature re: NBOT and CH.

CMS received a total of 65 comments including four that referenced the 2009 Cohen JAMA article. We took into consideration all comments as part of our assessment, weighing evidence-based references heavily.

As we noted in the background section, oxygen treatment can be associated with adverse events in some settings. Though the prevalence of CH is thought to be the same in the Medicare population as in other populations, Medicare beneficiaries have more comorbidities which may interfere with the relationship between CH and various modes of treatment. This is especially true in the Medicare population since oxygen therapy may have a direct impact on treatment of more common co-morbidities affecting this group. As noted earlier, though oxygen is often thought of as being harmless, it can have adverse effects on certain groups (Patel 2003). Patients suffering with advanced chronic obstructive pulmonary disease (COPD) can have suppression of their respiratory drive (Tinits 1983; Kleen, Messmer 1996). Patients with chronic left ventricular systolic dysfunction (LVSD) may have decreased cardiac output, decreased heart rates, as well as increased systemic vascular resistance (Park et 2010). All of these comorbidities could result in cardiac compromise with NBOT. Patients with COPD as well as LVSD are more likely to be in the Medicare population. There is insufficient evidence in the medical literature indicating that oxygen use is safe in Medicare patients with CH and other co-morbidities. Large studies are needed to confirm its safety in this group.

There is the potential for providing significant benefit to Medicare beneficiaries via home use of oxygen for CH. In this memorandum we have mentioned numerous limitations of available medical literature. Preventive as well as maintenance therapies for cluster headaches include the use of ergotamine derivatives, as well as other medications (e.g., tryptans). Breakthrough attacks are common, and can be incapacitating. They require other treatment strategies. Because of the limited number of options available for acute attacks, many clinicians have advocated the use of oxygen. Anecdotal reports abound noting that high flow oxygen seems to abort CHs, relieving pain and allowing patients to resume a more normal life. A CSP trial would help to determine if this treatment is successful, thus providing a significant benefit to the Medicare population.

A number of barriers exist to conducting clinical trials to address the evidentiary gaps. One barrier is related to the very nature of CH. Symptoms of CH are very intense and it is difficult to predict the onset of an episode. At onset, a patient may be in a location where oxygen is not readily available, such as public transportation or a typical work environment. We also note that, in contrast to a brand name drug having a single manufacturer, oxygen is furnished by diffused community based suppliers whose location and market interests may not provide incentives to conduct clinical research. Because CH is not common, individual investigators may find it challenging to enroll a large number of subjects in a clinical trial.

In summary, the randomized clinical trials have significant methodologic limitations that lessen their evidentiary weight. We believe that the evidence of benefit is not adequately generalizable to the Medicare beneficiary population, largely due to the underrepresentation of patients aged 65 years and older in the published studies. We are also concerned that the home use of oxygen may cause significant harm if used in patients who have cardiopulmonary comorbidities that are more commonly found in older persons. This tempers our ability to favorably consider the applicability to the Medicare population of various guidelines that are based on this fragile evidentiary foundation.

As a result of the large number of significant limitations in the studies we reviewed, as well as evidence of possible harms with home oxygen use in Medicare beneficiaries with comorbidities, we propose in response to question "a" that the evidence is not adequate to conclude that the home use of oxygen improves health outcomes in Medicare beneficiaries with cluster headache. Since the answer to "a" is no, we will not address question "b" as it is moot.

We therefore propose that the home use of oxygen is not reasonable and necessary under section 1862(a)(1)(A) of the Act but is appropriate for CED/CSP under 1862(a)(1)(E) of that Act.

1862(a)(1)(E) Analysis

As we noted above in this section, for some items or services, CMS may determine that the evidence is preliminary and not sufficient for Medicare coverage under section 1862(a)(1)(A), but, if the following criteria are met CED/CSP might be appropriate:

- The evidence includes assurance of basic safety;
- The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and
- There are significant barriers to conducting clinical trials.

Using CED/CSP trials can aid in determining the impact of NBOT on outcomes in patients with CHs. Protocols will be used to determine eligibility for the trial. Patients will be monitored closely by virtue of participating in the trial, and safeguards will be put in place to make sure that patients are safe and will adhere to the protocol. Patient safety in CED/CSP studies is addressed in the section of standards of scientific integrity and relevance to the Medicare population described in f) and g) of our proposed decision.

Of particular relevance to the Medicare beneficiary population is the possibility that patients who have CH may have comorbidities that would increase the risks of oxygen therapy. Thus we believe that a decision to administer home oxygen is not inconsequential clinically, and must be balanced by an expectation of clinical benefit.

As discussed previously, there is the potential for providing significant benefit to Medicare beneficiaries via home use of oxygen for CH. We do believe that the current evidence indicates that oxygen therapy is a promising treatment alternative for patients who suffer from cluster headaches, and that in some patients it may be preferable to the currently available pharmacologic therapies. We emphasize that breakthrough attacks are common, and can be incapacitating. They often require other treatment strategies. Because of the limited number of treatment options available for acute CH attacks, we have good reason to believe that access to NBOT under CED/CSP will be a substantial benefit to Medicare beneficiaries and would help to determine if this treatment is effective for CH. Again, relieving their pain and allowing them to resume a more normal life is a significant benefit to them.

To overcome barriers to conducting clinical trials of oxygen for treatment of CH, CMS is proposing CED/CSP. By providing coverage through CED/CSP, CMS hopes to determine if CH treatment with NBOT improves health outcomes. Therefore we believe that the evidence is sufficient to conclude that home use of oxygen is reasonable and necessary only under Coverage with Evidence Development/Coverage with Study Participation under section 1862(a)(1)(E) of the Act.

In light of the limitations of the current evidence base which make it challenging to exclude significant methodologic bias, we believe that an approved prospective clinical study under CED should include randomization. Subjects should be enrolled based on contemporary diagnostic criteria for cluster headache, and a clinically appropriate comparator should be used. As the ultimate course of CH may not be apparent early in the condition, i.e. spontaneous remission is possible, patients should have sufficient history to establish disease chronicity.

Therefore, enrolled Medicare beneficiaries should have had at least five severe to very severe unilateral headache attacks lasting 15-180 minutes when untreated. The headaches must be accompanied by at least one of the following findings:

1. ipsilateral conjunctival injection and/or lacrimation; or
2. ipsilateral nasal congestion and/or rhinorrhea; or
3. ipsilateral eyelid edema; or
4. ipsilateral forehead and facial sweating; or
5. ipsilateral miosis and/or ptosis; or
6. a sense of restlessness or agitation.

We believe that an approved study should reflect real world treatment patterns and assess clinically meaningful outcomes that correlate with a patient's ability to resume normal activities of daily living. The study should also provide information that will inform physician recommendations by identifying such factors that may predict a good or bad response to oxygen treatment. Thus, the home use of oxygen to treat CH is covered by Medicare only for beneficiaries with CH participating in an approved prospective clinical study comparing normobaric 100% oxygen with at least one clinically appropriate comparator for the treatment of CH. The clinical study must address one or more aspects of the following questions:

1. Prospectively, compared to individuals with cluster headache who do not receive NBOT, do Medicare beneficiaries with CH who receive NBOT have improved outcomes as indicated by:
    a. Pain relief
    b. Time to pain relief
    c. Durability of pain relief
2. Prospectively, among Medicare beneficiaries with cluster headache, which method of oxygen delivery provides the most benefit as indicated by:

a. Pain relief
b. Time to pain relief
c. Durability of pain relief

3. Prospectively, among Medicare beneficiaries with cluster headache, what other factors, if any, predict the patient's response to 100% oxygen therapy as indicated by:
   a. Pain relief
   b. Time to pain relief
   c. Durability of pain relief

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

(http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

IX. Conclusion:

CMS proposes that the evidence does not demonstrate that the home use of oxygen to treat cluster headache improves health outcomes in Medicare beneficiaries with cluster headache (CH). Therefore, we propose that home use of oxygen to treat CH is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act). However, we believe the available evidence suggests that the home use of oxygen to treat CH is promising and supports further research under §1862(a)(1)(E) of the Act through the Coverage with Study Participation (CSP) form of Coverage with Evidence Development (CED).

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

This decision does not, aside from the use of home oxygen to treat cluster headache, modify the existing requirements for coverage of oxygen currently identified in Section 240.2 and Section 240.2.1. The scope of this proposed decision does not include any consideration of hyperbaric oxygen (HBO) for any indication.

We are requesting public comments on this proposed determination pursuant to section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

APPENDIX A

Epidemiological studies of Cluster Headache

Author	Year	Journal	Country	Dx confirmed	Age	Sex	Population sample	# CH	% Prevalence
Ekbom et al.	1978	Headache	Sweden	Yes	<=18	Men	9803	9	.09
D'Alessandro et al.	1986	Cephalalgia	San Marino [	Yes	All	Both	21792	14	.07
Swanson et al.	1994	Neurology	USA	No	All	Both	6476	26	.40
Tonon et al.	2002	Neurology	San Marino	Yes	All	Both	26628	15	.06
Sjaastad	2003	Cephalalgia	Norway	Yes	18–65	Both	1838	7	.38
Ekbom et al.	2006	Neurology	Sweden	Yes	All	Both	31750	48	.15
Torelli et al.	2005	Neurology	Italy	Yes	18–65	Both	6500	13	.20

Torelli et al.	2006	Acta Biomed	Italy	Yes	<=14	Both	10071	21	.28
Katsarava et al.	2007	Cephalalgia	Germany	Yes	18–65	Both	3336	4	.12
Evers et al.	2007	J Neurol Neurosurg Psychiatry	Germany [	Yes	25–75	Both	2291	2	.15

APPENDIX B

General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).

- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

[1] Intensity of pain
Degree of pain usually expressed in terms of its functional consequence and scored on a verbal 5-point scale: 0, no pain; 1, mild pain, does not interfere with usual activities; 2, moderate pain, inhibits but does not wholly prevent usual activities; 3, severe pain, prevents all activities; 4, very severe pain. It may also be expressed on a visual analogue scale. http://ihs-classification.org/en/02_klassifikation/06_glossar/?letter=i

[2] Though the true biochemical cause of CH is not known, it is felt that the headaches occur when the trigeminal nerve is activated. When activated, the trigeminal nerve causes eye pain, as well as activation of other nerves affecting the eye causing nasal congestion, redness, and tearing. Hypothalamic involvement has been theorized as a component of CHs. This peripheral hypothesis has been supported by the ability of sumatriptan to rapidly abort most attacks, and trigeminovascular activation to mimic typical attacks. Leroux (2008).

[3] Neuroendocrine dysfunction in CH includes a primary central nervous system dysfunction with hypothalamic involvement (Leone 1990).

[4] Vegetative disturbance components of CH consist of tearing of the eye, watering of the nose, or sweating of the face with flushing (Thomas 1966).

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